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WHO Technical Report Series
903

WHO EXPERT COMMITTEE ON DRUG DEPENDENCE

Thirty-second Report

World Health Organization
Geneva 2001

WHO Library Cataloguing-in-Publication Data

WHO Expert Committee on Drug Dependence (2000 . Geneva, Switzerland)
Expert Committee on Drug Dependence : thirty-second report.

(WHO technical report series ; 903)

1.Psychotropic drugs — classification 2.Psychotropic drugs — pharmacology
3.Stereoisomerism 4.Treaties 5.Guidelines I.Title II.Series

ISBN 92 4 120903 8 (NLM classification : WM 270)
ISBN 0512-3054

Typeset in Hong Kong
Printed in Singapore
2001/13809 — Best-set/SNP — 7000

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Geneva, 12–15 September 2000

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1. Introduction

The WHO Expert Committee on Drug Dependence met in Geneva from 12 to 15 September 2000. The meeting was opened by Dr Y. Suzuki, Executive Director, Health Technology and Pharmaceuticals, who emphasized the significant role played by the Committee in the international drug control system. Implementation of the international drug control conventions is conducted under the auspices of the United Nations system as a whole. Within this framework, WHO undertakes medical and scientific evaluations of dependence-producing drugs and makes recommendations to the United Nations Commission on Narcotic Drugs concerning the level of international control to be applied to them. As WHO alone has responsibility for this function, no drug can be controlled internationally without prior evaluation by WHO. Within WHO, the task of evaluating dependence-producing drugs has been entrusted to the Committee since WHO was founded in 1948. Dr Suzuki also stressed the importance of balancing the need for preventing diversion through appropriate controls against the need for ensuring easy access when assessing therapeutic substances with abuse potential.

2. Revision of guidelines

In order to implement a consistent and systematic review process, in 1986 WHO developed a formal procedure for its review of dependence-producing psychoactive substances. This procedure was revised in 1990. The Committee was informed by the Secretariat that, as recommended at the previous meeting of the Committee (*1*), the 1990 guidelines for its review of dependence-producing psychoactive substances had been revised. The new guidelines, which were adopted by the Executive Board at its 105th session in January 2000 (*2*), reflect the developments that have taken place in the international drug control system since 1990.

One of the main changes introduced by the new guidelines is the clarification provided concerning the roles of the 1988 United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances (*3*; hereinafter referred to as "the 1988 Convention") and of the 1971 Convention on Psychotropic Substances (*4*; hereinafter referred to as "the 1971 Convention"). In the past the Committee had noted that questions of overlapping jurisdiction between the 1971 and 1988 Conventions had hindered fully effective international regulation (*1*). The new guidelines thus provide practical guidance for avoiding unnecessary duplication of controls under the two

Conventions. One specific requirement in this regard is discussed in more detail in section 3.1 in relation to the scheduling of ephedrine. Similar guidance is given with regard to the relationship between the 1988 Convention and the 1961 Single Convention on Narcotic Drugs (*5*; hereinafter referred to as "the 1961 Convention"). The successful application of the new guidelines will require further strengthening of coordination between WHO and the International Narcotics Control Board (INCB), which is given the mandate to formulate scheduling recommendations with regard to chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances under the 1988 Convention.

Other than this, the principles of the review procedure, including the scheduling criteria, remain unchanged. Other changes in the new guidelines are organizational in nature, and include the following:

— clarification of the function of the Committee and that of the Secretariat;
— rationalization of the structure of the guidelines according to the sequence of events in the review process;
— clarification concerning the publication of documents, including the electronic publication on the Internet of scheduling recommendations.

3. Matters pending since the thirty-first meeting of the Committee

3.1 Scheduling of ephedrine under the new guidelines

The Committee conducted a critical review of ephedrine at its previous meeting in 1998 and recommended that (–)-ephedrine[1] and (±)-ephedrine[2] be placed in Schedule IV of the 1971 Convention (*1*). However, at its forty-second session in 1999 (*6*), the Commission on Narcotic Drugs decided not to vote on this recommendation, but requested that WHO, in consultation with the INCB, as appropriate, undertake for its consideration a further review of (–)-ephedrine and (±)-ephedrine.

The medical and scientific aspects of the review of ephedrine conducted by the Committee at its previous meeting were considered to be still valid. However, this critical review was carried out in conformity with the 1990 guidelines. As outlined in section 2, the new guidelines provide clear guidance for the scheduling of a psycho-

[1] (1*R*,2*S*)-2-methylamino-1-phenylpropan-1-ol.
[2] (1*RS*,2*SR*)-2-methylamino-1-phenylpropan-1-ol.

tropic substance under the 1971 Convention when that substance is also subject to control as a chemical frequently used in the illicit manufacture of narcotic drugs and psychotropic substances under the 1988 Convention.

Thus, the further review of ephedrine, as requested by the Commission on Narcotic Drugs, requires a careful re-evaluation of the previous recommendation in the light of these new guidelines.

The new guidelines (*2*) require that in the case of a review of a psychoactive substance which is already included in Table I or Table II of the 1988 Convention (such as ephedrine) or has already been recommended by INCB for inclusion therein, the Expert Committee should be guided by three principles, including that any proposal for a change in the existing status of the substance should be made only if specific new control measures are necessary in order to decrease the extent or likelihood of abuse, and will not unduly limit its availability for legitimate medical and scientific purposes.

At the time of the 1998 review, six countries reported ephedrine abuse of some significance in response to a WHO questionnaire. Subsequently, similar information was received from a delegation of another country. As of the time of the present meeting, in response to a follow-up questionnaire, none of these seven countries have indicated the need for additional control measures, since those introduced in the past have been successful.

At its present meeting, the Committee was unable to identify specific new control measures that would, in its opinion, decrease the current level of ephedrine abuse. The Committee therefore recommended withdrawal of the 1998 recommendation concerning the placement of ephedrine in Schedule IV of the 1971 Convention on the grounds that WHO, as of the time of the present meeting, has no information to satisfy the requirements specified in the new guidelines for recommending international control of ephedrine under the 1971 Convention.

3.2 Interpretation guidelines concerning the control status of stereoisomers

At its thirty-first meeting (*1*), the Committee reviewed a proposal submitted by the Government of Spain to extend international control of psychotropic substances in Schedules I and II of the 1971 Convention to include their isomers, esters, ethers and "analogues".[1]

[1] In this context an "analogue" is defined as "any modified chemical compound producing effects similar to those produced by the original substance".

It recommended that a phrase be added to Schedule I of the 1971 Convention to clarify the scope of the control of stereoisomers. The Commission on Narcotic Drugs adopted this recommendation at its forty-second session in March 1999 (*6*). In addition, with regard to stereoisomers of substances listed in Schedules II, III and IV of the 1971 Convention, the Commission on Narcotic Drugs decided that interpretation guidelines should be developed by WHO, in collaboration with INCB, in order to eliminate the confusion arising from the inconsistencies in the present nomenclature in those Schedules.

The Committee was presented with the draft interpretation guidelines produced by a group of experts convened jointly by INCB and WHO in September 2000. The Committee agreed that these guidelines, which are annexed to this report, would provide adequate clarification concerning the scope of control of stereoisomers of psychotropic substances listed in Schedules II, III and IV of the 1971 Convention. However, the Committee considered that it would be useful to include some further explanatory text to clarify the meanings of the technical terms used in the guidelines, especially if the target audience was likely to include non-specialists.

The Committee recommended that, whenever possible, scientific information be obtained on the abuse potential of all stereoisomers of pharmaceutical products proposed for listing in Schedules II, III and IV of the 1971 Convention. The Committee noted, however, that lack of resources may make full implementation of this recommendation difficult.

The Committee agreed that inconsistencies in the chemical designations of several substances listed in the 1971 Convention, including amphetamine and methamphetamine stereoisomers, may not be directly resolved by the application of the interpretation guidelines.

The Committee recommended that WHO carefully monitor the implementation of the interpretation guidelines and take appropriate action if warranted, especially in view of the present tendency in stereochemical nomenclature to replace older forms of notation.

4. Critical review of psychoactive substances

4.1 Critical review

Critical review of psychoactive substances is conducted by the Committee in any of the following cases: (1) there has been notification from a Party to the 1961 or the 1971 Convention concerning the scheduling of a substance; (2) there has been an explicit request from the Commission on Narcotic Drugs to review a substance; (3) pre-

review of a substance has resulted in a recommendation for critical review; (4) information is brought to the attention of WHO that a substance of especially serious risk to public health and society and of no recognized therapeutic use by any Member State is clandestinely manufactured. If therapeutic use of the substance is confirmed subsequently by any Member State in respect of case (4), the substance shall be subjected to a pre-review.

Out of the six substances under critical review at the present meeting, five were pre-reviewed and recommended for critical review at the previous meeting of the Committee (*1*). The remaining substance, 4-methylthioamphetamine (4-MTA), was proposed by the Secretariat as being a substance meeting condition (4) in the preceding paragraph. In reaching a decision on the scheduling of these substances, the Committee used the following criteria (see sections 4.2 and 4.3), in accordance with the new guidelines referred to in section 2.

4.2 Scheduling criteria for narcotic drugs

The Committee, when reviewing the abuse liability of dependence-producing drugs which fall within the terms of the 1961 Convention, first decides whether the substance under review has morphine-like, cocaine-like or cannabis-like effects, or is convertible into a scheduled substance having such effects. If either of these conditions is fulfilled, the Committee then determines if the substance:

— is liable to similar abuse and produces similar ill effects to the substances in Schedule I or II; or
— is convertible into a substance already in Schedule I or II.

4.3 Scheduling criteria for psychotropic substances

If the Committee finds that the psychoactive substance under review does not meet the criteria described above and cannot therefore be appropriately controlled under the 1961 Convention, it makes its recommendations in terms of the 1971 Convention. In considering scheduling under the 1971 Convention, the Committee determines whether:

— the substance has the capacity to produce (a) a state of dependence, and (b) central nervous system stimulation or depression, resulting in hallucinations or disturbances in motor function, thinking, behaviour, perception or mood; or
— the substance has the capacity to produce similar abuse and similar ill effects to a substance in Schedule I, II, III or IV; and

— there is sufficient evidence that the substance is being or is likely to be abused so as to constitute a public health and social problem, warranting its placement under international control.

Additional, more specific, criteria are used for proposing the inclusion of a substance for control in a particular Schedule; these were first developed by the Committee at its seventeenth meeting in 1969 (*7*) and are as follows:

- Schedule I. Substances whose liability to abuse constitutes an especially serious risk to public health and which have very limited, if any, therapeutic usefulness.
- Schedule II. Substances whose liability to abuse constitutes a substantial risk to public health and which have little to moderate therapeutic usefulness.
- Schedule III. Substances whose liability to abuse constitutes a substantial risk to public health and which have moderate to great therapeutic usefulness.
- Schedule IV. Substances whose liability to abuse constitutes a smaller but still significant risk to public health and which have little to great therapeutic usefulness.

In cases where the above criteria apply only in part, the scheduling recommendation should be made with a higher regard to the risk to public health than to therapeutic usefulness. However, recommendations for inclusion in Schedule I should be made only when the above criteria are fully met, with respect to both therapeutic usefulness and the risk to public health.

Examples of psychotropic substances in the four Schedules of the 1971 Convention are:

- Schedule I: (+)-lysergide (LSD), mescaline, 3,4-methylenedioxy-*N*-methylamphetamine (*N*-α-dimethyl-3,4-(methylenedioxy)phenethylamine; MDMA), psilocine (27 substances in total).
- Schedule II: amphetamines, methylphenidate, secobarbital (15 substances in total).
- Schedule III: amobarbital, flunitrazepam, pentobarbital (9 substances in total).
- Schedule IV: most benzodiazepines, pemoline, phenobarbital (60 substances in total).

4.4 Review of substances

4.4.1 *4-Bromo-2,5-dimethoxyphenethylamine (2C-B)*

Substance identification

4-Bromo-2,5-dimethoxyphenethylamine (2C-B), chemically 2-(4-bromo-2,5-dimethoxyphenyl)ethylamine (CAS 66142-81-2). Other

names include 4-bromo-2,5-dimethoxy-beta-phenethylamine (BDMPEA), "Erox", "MFT", "Nexus" and "Performax". There are no chiral centres; therefore, no stereoisomers or racemates are possible.

Previous review

In 1998, at its thirty-first meeting (*1*), the Committee pre-reviewed 2C-B and recommended critical review.

Similarity to known substances and effects on the central nervous system

2C-B is structurally and pharmacologically similar to brolamfetamine and mescaline. It acts as a selective partial agonist for 5-HT_{2A} and 5-HT_{2C} serotonin receptors. In humans, 2C-B is more potent than mescaline but less potent than brolamfetamine. At low doses it enhances skin sensitivity and responsiveness to smells and tastes. At high doses it is a strong hallucinogen, producing particularly marked visual hallucinations with an intense colour play, intriguing patterns emerging on surfaces and distortions of objects and faces. 2C-B is also reported to enhance sexual feelings, perception and performance.

Dependence potential

There have been no studies in animals or humans on the dependence potential of 2C-B.

Actual abuse and/or evidence of likelihood of abuse

During the 1990s, 2C-B was sold as an aphrodisiac in several countries and abuse of 2C-B has been reported by a number of countries. This suggests that 2C-B, like many other hallucinogens, has modest abuse liability. Although hallucinogens are rarely associated with compulsive use or dependent use, they are known to have modest abuse potential, particularly among polydrug abusers.

Therapeutic usefulness

Apart from its controversial experimental use in psychotherapy, 2C-B, like most other hallucinogens, does not have any known therapeutic usefulness.

Recommendation

Although the available studies on 2C-B are limited, it has been shown to be chemically and pharmacologically similar to the hallucinogen mescaline. The altered state of mind induced by hallucinogens such as 2C-B may result in harm to the user and to others. On the basis of its perceived aphrodisiac effects and the known modest abuse potential of hallucinogenic drugs in general, it is estimated that 2C-B may be

abused so as to constitute a public health and social problem, warranting its placement under international control. The Committee noted, however, that hallucinogens are rarely associated with compulsive use and that abuse of 2C-B has been infrequent, suggesting that the drug is likely to constitute a substantial, rather than an especially serious, risk to public health. For these reasons, the Committee recommended that 2C-B be placed in Schedule II of the 1971 Convention.

4.4.2 *4-Methylthioamphetamine (4-MTA)*

Substance identification

4-Methylthioamphetamine (CAS 14116-06-4) is also known as 4-MTA. Other names include "MK", α-methyl-4-methylthiophenethylamine, "MTA", *p*-methylthioamphetamine (*p*-MTA), "S5", "Flatliner" and "The One and Only Dominator". 4-MTA has one chiral centre and can exist as two enantiomers and a racemate. To date, only the racemic mixture has been reported to have been synthesized.

Previous review

4-MTA has not been pre-reviewed by the Committee. However, the Committee decided to undertake a critical review of 4-MTA because it met the requirements for critical review specified in section 4.1, item (4).

Similarity to known substances and effects on the central nervous system

4-MTA is structurally similar to 4-methoxyamphetamine and is both a potent serotonin-releasing agent and a reversible inhibitor of monoamine oxidase A (MAO-A). Pharmacologically, it is similar to tenamfetamine (methylenedioxyamphetamine or MDA) and MDMA; studies suggest that 4-MTA is six times as potent as these substances in inhibiting 5-HT uptake.

Dependence potential

Drug discrimination studies in rats suggest that 4-MTA produces discriminative stimulus effects similar to MDMA. However, 4-MTA did not substitute for amphetamines, LSD or phencyclidine. Reports from the United Kingdom indicate that 4-MTA, like MDMA, is abused for its stimulant/euphoric effects (a "rush").

Actual abuse and/or evidence of likelihood of abuse

4-MTA is abused mainly in Europe, where it appears to be part of the dance music culture. However, it is likely that its use is less widespread than it otherwise might be because of perceptions among users

that the drug is stronger and more harmful than other "club drugs", such as MDMA. Abuse of 4-MTA has resulted in a number of fatalities and hospital admissions. It appears that toxic effects can be produced directly from the drug, and that the presence of other drugs or alcohol may exacerbate such effects.

Therapeutic usefulness

4-MTA has no recognized therapeutic use.

Recommendation

4-MTA is chemically and pharmacologically similar to 4-methoxyamphetamine, MDA and MDMA. It is a relatively new synthetic drug, and was seized for the first time in 1997. Although evidence of its actual abuse is available only in several European countries, recent seizures, including those of large quantities reported from a wider range of countries, suggest that trafficking and abuse of 4-MTA have become more widespread. On the basis of this information and its similarity to known MDA-type drugs, as well as drug discrimination studies in animals, it is estimated that 4-MTA is likely to be abused so as to constitute a public health and social problem, warranting its placement under international control. Taking into consideration that 4-MTA has no recognized therapeutic use and that it has caused a number of fatalities, the Committee concluded that abuse of 4-MTA represents an especially serious risk to public health. The Committee therefore recommended that 4-MTA be placed in Schedule I of the 1971 Convention.

4.4.3 *Gamma-hydroxybutyric acid (GHB)*

Substance identification

Gamma-hydroxybutyric acid (GHB, 4-hydroxybutyric acid) usually exists as either the free acid (CAS 591-81-1) or as the sodium salt, sodium oxybate[1] (CAS 502-85-2). There are no chiral centres; therefore, no stereoisomers or racemates are possible.

Previous review

In 1998, at its thirty-first meeting (*1*), the Committee pre-reviewed GHB and recommended critical review. The Committee also recommended critical review of gamma-butyrolactone (GBL), but the scarcity of data on its abuse precluded critical review at the present meeting.

[1] National nonproprietary name.

Similarity to known substances and effects on the central nervous system

GHB is an endogenous compound and is structurally similar to the neurotransmitter gamma-aminobutyric acid (GABA). It produces sedative and anaesthetic effects when administered at high doses. Its depressant effects are different from those produced by barbiturates and benzodiazepines and appear to be associated with its cataleptic effects. GHB possesses distinct excitatory properties, which may be due to its effect on the dopaminergic system (it increases intracellular neuronal dopamine). GHB has been found to induce anaesthesia (but does not provide pain relief), slow-wave sleep, bradycardia, vomiting, random clonic movements, hypothermia, a reduction in potassium levels, a decrease in ventilatory rate and apnoea (although the respiratory centre remains sensitive to increases in carbon dioxide levels).

Dependence potential

In drug discrimination studies in animals, none of the known abused drugs have been demonstrated to fully substitute for GHB. Morphine, dexamfetamine, LSD and some benzodiazepines produced, at best, partial substitution.

There have been few studies on the dependence/abuse potential of GHB in humans. However, numerous studies have been conducted in which GHB was administered to patients at varying concentrations. No dependence was observed at low doses, but a withdrawal syndrome (characterized by insomnia, muscular cramping, tremors and anxiety) was reported in some cases following cessation of long-term administration of high doses.

Actual abuse and/or evidence of likelihood of abuse

GHB abuse has been reported in many regions, including Australia, Europe and the USA. Precursors of GHB (e.g. GBL and 1,4-butanediol), which are metabolized to GHB in the body, have also been abused. Although initially abused by body-builders for its apparent growth hormone-promoting properties, the more recent primary mode of abuse worldwide has been the use of GHB for its subjective hypnotic, euphoric and hallucinogenic effects, especially in the context of the dance music culture (i.e. "raves"). Some users have claimed to use GHB as an alternative to alcohol (for relaxation), as a sexual adjunct, as an appetite suppressant or as an anti-ageing product. It has also been implicated in cases of sexual assault.

It appears that toxic effects can be produced directly from GHB and that the presence of other depressant or sedative drugs (e.g. opiates, benzodiazepines, alcohol and barbiturates) and possibly other psy-

choactive compounds (e.g. amphetamines) may exacerbate these effects. Hospital admissions and deaths have been linked to GHB ingestion and generally involve the onset of coma and respiratory depression.

Therapeutic usefulness

GHB has been used as an anaesthetic agent and as an aid to alcohol/opiate withdrawal, primarily in France, Germany and Italy, respectively. In Canada and the USA it is currently under investigation for the treatment of narcolepsy-associated cataplexy.

Recommendation

Although GHB is endogenous in the human body, it has psychoactive and toxic effects when administered. The pattern and consequences of its abuse in a number of countries in Europe and the USA seem to suggest that its liability to abuse constitutes a significant risk to public health. Its recent abuse is attributed, at least in part, to the current easy availability of GHB and some of its precursors, a factor that is likely to be reduced once GHB is placed under international control. For these reasons, the Committee recommended that GHB be placed in Schedule IV of the 1971 Convention.

4.4.4 *N-Methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB)*

Substance identification

N-Methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB) or 2-(methylamino)-1-(3,4-methylenedioxyphenyl)butane (CAS 103818-46-8) is also known as "EDEN" and "Methyl-J". MBDB has one chiral centre and can exist as two enantiomers and as a racemate.

Previous review

In 1998, at its thirty-first meeting (*1*), the Committee pre-reviewed MBDB and recommended critical review.

Similarity to known substances and effects on the central nervous system

In the rat, MBDB causes serotonergic neurotransmission effects similar to those seen after administration of MDMA; it also increases locomotor activity and decreases exploratory behaviour. Clinical studies have shown that MBDB has subjective effects similar to, but less potent than, MDMA.

Dependence potential

There have been no studies in animals or humans on the dependence potential of MBDB. However, drug discrimination studies have shown that rats can distinguish both MBDB and MDMA from

stimulants such as amphetamine, methamphetamine and cocaine and comparative hallucinogens such as 4-methyl-2,5-dimethoxyamphetamine (DOM), LSD and mescaline. The results of a pilot study have suggested that MBDB has less stimulant activity than MDMA. This finding has been confirmed by further studies involving both drugs. Whereas high doses of racemic MDMA completely substituted for amphetamine, *S*-MBDB demonstrated only partial substitution. Furthermore, in conditioned place preference testing in animals, MBDB was found to have only about 40% of the stimulant activity of MDMA. Reports on subjective effects in humans also suggest that MBDB produces less euphoria than MDMA.

Actual abuse and/or evidence of likelihood of abuse

The abuse of MBDB was first reported in Europe during the first half of the 1990s. Recent reports of seizures of the drug from several European countries suggest that trafficking of MBDB may be decreasing, after having reached a peak during the latter half of the 1990s.

Therapeutic usefulness

MBDB has no recognized therapeutic usefulness.

Recommendation

Although MBDB is both structurally and pharmacologically similar to MDMA, the limited available data indicate that its stimulant and euphoriant effects are less pronounced than those of MDMA. There have been no reports of adverse or toxic effects of MBDB in humans. Law enforcement data on illicit trafficking of MBDB in Europe suggest that its availability and abuse may now be declining after reaching a peak during the latter half of the 1990s. For these reasons, the Committee did not consider that the abuse liability of MBDB would constitute a significant risk to public health, thereby warranting its placement under international control. Scheduling of MBDB was therefore not recommended.

4.4.5 ***Diazepam (INN)***

Substance identification

Diazepam is chemically 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (CAS 439-14-5). It is marketed under numerous trade names.

Previous review

In 1984, 33 benzodiazepines (including diazepam) were placed in Schedule IV of the 1971 Convention. In 1990, at its twenty-seventh

meeting (*8*), the Committee reassessed all benzodiazepines in schedule IV, at which time it was noted that diazepam and flunitrazepam showed a continuing higher incidence of abuse and association with illicit activities. The Committee therefore recommended that WHO continue to keep diazepam and flunitrazepam under surveillance in order to determine whether they merit being placed under critical review.

In 1998, at its thirty-first meeting (*1*), the Committee pre-reviewed several benzodiazepines and concluded that flunitrazepam, diazepam and injectable dosage forms of temazepam might have greater abuse liabilities than the other benzodiazepines. Of these three benzodiazepines, the Committee recommended critical review of diazepam only, because flunitrazepam had already been rescheduled to Schedule III and the higher abuse liability of temazepam applied only to its injectable preparation, the availability of which was geographically limited.

Similarity to known substances and effects on the central nervous system

Diazepam belongs to the benzodiazepine group of substances and has anxiolytic, sedative–hypnotic, anticonvulsant and muscle relaxant effects.

Dependence potential

Studies in both animals and humans have demonstrated that diazepam has reinforcing efficacy and can produce withdrawal symptoms upon discontinuation of long-term use. The reinforcing/subjective effects of various benzodiazepines were compared in a series of experimental studies in subjects with a history of drug abuse, the results of which indicated that diazepam produces greater reinforcing or subjective effects than several of the other benzodiazepines studied.

Actual abuse and/or evidence of likelihood of abuse

Significant abuse of diazepam has been reported worldwide, both in the past and recently. Various studies based on surveys in drug-using populations indicate that flunitrazepam and diazepam are often the preferred benzodiazepines and several epidemiological studies, which have adjusted for drug availability, suggest that rates of abuse of diazepam exceed those of most other benzodiazepines. Nevertheless, examination of reports of dependence from the WHO Adverse Drug Reaction database, adjusted for global consumption, showed that diazepam abuse rates are not as high as those for alprazolam and lorazepam.

Therapeutic usefulness

Diazepam is used widely in medicine, mainly as an anxiolytic sedative, anaesthetic and anti-convulsant. In particular, diazepam is an inexpensive and effective treatment for status epilepticus, a life-threatening condition. Its use is particularly important in developing countries where alternatives may be unavailable or unaffordable. Diazepam is included in the WHO Model List of Essential Drugs (*9*).

Recommendation

Experimental studies in humans, surveys and epidemiological studies indicate that diazepam has a greater abuse liability than many of the other benzodiazepines. The Committee also noted that certain other benzodiazepines, such as alprazolam and lorazepam, may be associated with greater abuse liability than diazepam. In view of the wide therapeutic usefulness of diazepam and its important role in medicine in developing countries in particular, the Committee decided that rescheduling of diazepam to a higher level of control is not currently warranted. However, the Committee recommended that WHO continue to keep diazepam under surveillance.

4.4.6 *Zolpidem (INN)*

Substance identification

Zolpidem is chemically *N,N*,6-trimethyl-2-*p*-tolylimidazo[1,2-*a*]pyridine-3-acetamide or *N,N*,6-trimethyl-2-(4-methylphenyl)imidazol[1,2-*a*]pyridine-3-acetamide (CAS 82626-48-0). It is marketed under the trade names Ambien, Bikalm, Niotal, Stilnoct and Stilnox.

Previous review

Zolpidem was pre-reviewed by the Committee at its twenty-ninth meeting in 1994 (*10*), at which time continued surveillance was recommended. The Committee pre-reviewed zolpidem again at its thirty-first meeting in 1998 (*1*), and recommended critical review in 2000, on the grounds that a greater number of reports on its abuse liability would be available by that date.

Similarity to known substances and effects on the central nervous system

Though chemically different from the benzodiazepines, zolpidem produces benzodiazepine-like effects, especially hypnotic effects. It acts as an agonist, binding with high and low affinity to BZ_1 and BZ_2 receptor subtypes, respectively.

Dependence potential

The results of laboratory studies in humans suggest that zolpidem and triazolam are generally similar in terms of producing reinforcing/

subjective effects. As with many of the benzodiazepines, there have been a number of case reports describing withdrawal symptoms after cessation of zolpidem administration. Although such symptoms do not necessarily lead to compulsory drug-taking (drug dependence) in humans, there are reports of clinically diagnosed cases of drug dependence resulting from prolonged use of zolpidem.

Actual abuse and/or evidence of likelihood of abuse

Epidemiological studies indicate that zolpidem is associated with a relatively low incidence of abuse. While there have been sporadic reports of cases of zolpidem abuse in the scientific literature, these cases have typically involved patients with a history of drug abuse or chronic psychiatric disorders. Cases of zolpidem overdose requiring emergency treatment have been reported, but have rarely been fatal. Rates of actual abuse and dependence on zolpidem appear to be similar to those of other hypnotic benzodiazepines currently listed in Schedule IV. In terms of the numbers of cases of abuse, dependence and withdrawal syndrome reported to the WHO Adverse Drug Reaction database, less than 10 benzodiazepines are ranked higher than zolpidem.

Therapeutic usefulness

Zolpidem is used for the treatment of insomnia in more than 80 countries.

Recommendation

Although zolpidem has a somewhat novel neuropharmacological profile relative to classic benzodiazepines, studies suggest that its abuse potential may be comparable to that of many benzodiazepines. Furthermore, rates of actual abuse and dependence on zolpidem, as well as the risk to public health of its abuse, appear to be similar to those of the hypnotic benzodiazepines currently placed in Schedule IV. The Committee therefore recommended that zolpidem be placed in Schedule IV of the 1971 Convention.

5. Pre-review of psychoactive substances

Pre-review is a preliminary review carried out by the Committee in order to determine whether a psychoactive substance should be subjected to critical review in the context of its international control under either the 1961 or the 1971 Convention. The criterion for judging whether critical review is necessary is whether WHO has information that may justify the scheduling of the substance. Under the new guidelines (see section 2), in addition to the Secretariat, any

member of the Committee or representatives of other organizations invited to participate in the Committee meeting can submit a proposal (with supporting information) to pre-review a substance.

5.1 Amfepramone (INN)

Amfepramone (also called "diethylpropion") is an amphetamine-like anorectic drug with stimulant effects on the central nervous system. It was first reviewed in 1969 at the seventeenth meeting of the Committee (*7*), which recommended its inclusion in Schedule IV of the 1971 Convention. It was included in Schedule IV at the time of adoption of the 1971 Convention. At its thirty-first meeting in 1998 (*1*), the Committee recommended pre-review of amfepramone at a future meeting. Since then, very little new scientific information has become available on the drug. However, information presented to the Committee at its present meeting by the INCB indicates that abuse and illicit trafficking of amfepramone have been reported from nearly all regions of the world (Africa, the Americas, Asia and Europe), and became particularly widespread in Asia and the Russian Federation during the second half of the 1990s.

Recommendation

The Committee has previously determined that amfepramone has abuse liability that warrants its control in Schedule IV of the 1971 Convention. In response to recent reports of widespread abuse and illicit trafficking, the Committee recommended that a critical review be undertaken at such time that adequate information is available on the extent of public health and social problems associated with the increased illicit activities with amfepramone.

5.2 Amineptine (INN)

Amineptine is a tricyclic antidepressant that selectively decreases the uptake of dopamine without affecting norepinephrine and serotonin uptake. A few case reports of amineptine abuse or dependence from France, Italy, Pakistan, Singapore and Spain are described in the literature. In France, for example, 186 cases of amineptine abuse were reported to the Regional Centres of Pharmacovigilance or to the manufacturer during a 10-year period (1978–88). As of September 1999, the WHO Adverse Drug Reactions database had received 40 reports on amineptine abuse (ranked ninth in the list of all drugs for which abuse has ever been reported as an adverse drug reaction) and 106 reports on amineptine dependence (ranked eleventh in the list).

Prolonged and excessive use of the drug has been linked to a number of side-effects, including amineptine-induced acne. The sudoriparous

glands, which accumulate amineptine, show signs of direct toxicity. Amineptine therapy has also been associated with hepatic and pancreatic injury. These observations, together with the features of the cases published in the literature, suggest that amineptine can produce a wide spectrum of hepatic injuries, including hepatocellular necrosis, cholestasis, or a combination of both.

Recommendation

Unlike most antidepressants, amineptine elicits central nervous system stimulation by blockade of dopamine uptake. Abuse and/or dependence have been reported from France (where it is under national control), Italy, Pakistan and Spain. As there is a likelihood of amineptine being abused in other countries to such an extent as to constitute a significant public health and social problem, the Committee recommended it for critical review.

5.3 Buprenorphine (INN)

Buprenorphine is a partial μ-opioid agonist which is used as an analgesic and in the treatment of opioid dependence. It was reviewed by a WHO review group in 1983 (*11*), which did not recommend international control, although it recommended the inclusion of the pharmacologically related substance pentazocine in Schedule III of the 1971 Convention (see section 5.6). A critical review of buprenorphine was undertaken again in 1988 at the twenty-fifth meeting of the Committee (*12*), which recommended its placement in Schedule III of the 1971 Convention. In 1995, INCB requested that WHO undertake a revision of the control system for buprenorphine, in the light of new evidence of significant diversion and increasing abuse in some countries.

Abuse of buprenorphine sublingual tablets by opioid-dependent individuals has been widely reported in the literature. Abuse involves crushing the tablets, followed by intravenous injection. Intranasal administration and smoking have also been reported. According to INCB, the French authorities reported that in 1998 about 15% of the buprenorphine prescribed was diverted to the illicit market. INCB has also received information from governments indicating significant illicit traffic of buprenorphine in South Asia. In Bangladesh, India and Nepal, increasing abuse of buprenorphine first became evident in 1994; the levels of abuse continued to increase from 1995 to 1998. In Bangladesh, buprenorphine was reportedly abused by 90% of injecting drug abusers. Seizure figures indicated increased smuggling of buprenorphine injections from India to Bangladesh. Nepal also reported increased abuse and smuggling of buprenorphine injections.

In addition, smuggling or attempted smuggling of injectable buprenorphine of Indian origin has been reported from Armenia, Azerbaijan, Georgia and the Russian Federation. Abuse and/or seizures of buprenorphine have also been sporadically reported from other countries.

Recommendation

Buprenorphine acts as a partial agonist at μ-opioid receptors and as an antagonist at κ-opioid receptors. In this respect it is different from prototypical μ-opioid agonists such as morphine and methadone. However, the pattern of diversion and abuse of buprenorphine as reported to INCB indicates its similarity to opiates from an epidemiological point of view. It was also noted that the Committee at its twenty-fifth meeting did not provide an adequate pharmacological explanation about the psychotropic effects of buprenorphine nor a clear rationale for its decision to recommend control under the 1971 Convention rather than the 1961 Convention (*12*). In consideration of these issues and recent evidence of the increasing rates of abuse and illicit trafficking, the Committee recommended critical review of buprenorphine.

5.4 Carisoprodol (INN)

Carisoprodol is a centrally-acting skeletal muscle relaxant. It has not been reviewed previously by the Committee. Although the exact mechanism of its action is not known, studies in animals suggest that the drug preferentially depresses polysynaptic reflexes; high doses can depress monosynaptic reflexes. Several case reports of abuse or dependence have been described in the literature. In virtually all cases, carisoprodol was used in combination with other substances. Abuse of carisoprodol has been reported in Canada, India and the USA. In the USA, according to reports of the Drug Abuse Warning Network, carisoprodol was implicated in 45–48 deaths per year during the period 1992–94.

Recommendation

Sporadic abuse of carisoprodol is not a new phenomenon. There is no indication of any significant development in its abuse pattern, although some increase in its abuse has been reported by one country. The Committee did not therefore recommend critical review of carisoprodol.

5.5 Dronabinol (INN)

Dronabinol is the stereochemical isomer (*trans*-form) of delta-9-tetrahydrocannabinol (delta-9-THC). It was included in the original

list of substances in Schedule I of the 1971 Convention under the heading "tetrahydrocannabinols, all isomers". It was previously reviewed in 1990 at the twenty-seventh meeting of the Committee, which recommended that it be rescheduled from Schedule I to Schedule II (*8*). Although data on its therapeutic usefulness and dependence liability related only to one stereochemical variant of delta-9-THC (dronabinol), the Committee noted that making a distinction between this variant and other stereoisomers may create legal and forensic analytical problems in some countries. For this reason, the Committee recommended that dronabinol and its stereochemical variants be rescheduled together.

In the USA dronabinol is used therapeutically for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who fail to respond to conventional antiemetic treatments. Since its rescheduling to Schedule II of the 1971 Convention, the medical indications for dronabinol have been expanded to include the treatment of anorexia associated with weight loss in patients with the acquired immunodeficiency syndrome (AIDS).

Recommendation

In the absence of any evidence that individuals are taking dronabinol for non-medical use, the public health problems associated with dronabinol are currently considered to be only a potential risk. Dronabinol is not widely available, and diversion or off-label use has not been documented to be significant. Illicit manufacture of dronabinol or delta-9-THC has rarely been reported. Given that, irrespective of whether it is synthesized or isolated from the cannabis plant, delta-9-THC is considerably more expensive than its natural preparation (cannabis), its widespread abuse is unlikely. In the case of the existing pharmaceutical preparations of dronabinol, their delayed onset and longer duration of action relative to cannabis may be additional contributing factors limiting their abuse. The current scheduling of delta-9-THC is based on its therapeutic usefulness and the risk assessment made at the twenty-seventh meeting of the Committee in 1990 (*8*). The very low rate of actual abuse of delta-9-THC suggests that the risk to public health may actually be less than that required for the substances to be included in Schedule II. The Committee therefore recommended critical review of delta-9-THC.

5.6 Pentazocine (INN)

Pentazocine is an opioid agonist–antagonist analgesic. It was reviewed by a WHO review group in 1978, 1981 and 1983 (*11*, *13*, *14*). In recommending placement of pentazocine in Schedule III of the 1971

Convention at its meeting in 1983, the WHO review group noted the capacity of pentazocine to produce: (a) a state of dependence; and (b) central nervous system changes, resulting in disturbances in mood and behaviour. In 1984, pentazocine was placed in Schedule III of the 1971 Convention. However, at the Eighth Special Session of the Commission on Narcotic Drugs (*15*), an extensive debate took place, which resulted in a resolution requesting re-examination of the possibility of scheduling pentazocine under the 1961 Convention. In 1988, at its twenty-fifth meeting, the Committee concluded that scheduling was appropriate and recommended that pentazocine should remain in Schedule III of the 1971 Convention (*12*).

Recommendation

Pentazocine is a strong κ-agonist and has either weak μ-antagonist or partial agonist activity. Instead of euphoria, κ-agonists produce dysphoric psychotomimetic effects (disoriented and/or depersonalized feelings). Therefore, the recognition of psychotropic effects of pentazocine in previous assessments is appropriate. Furthermore, INCB has not received any information to suggest that the current control measures applicable to pentazocine are inadequate. The Committee did not therefore recommend critical review.

5.7 Poppy straw

Poppy straw is defined as "all parts (except the seeds) of the opium poppy, after mowing". Opium poppy means any plant of the species *Papaver somniferum* L. Poppy straw has not been previously reviewed by WHO. However, within the established framework of collaboration between INCB and WHO, the desirability of evaluating the abuse liability of poppy straw extracts was pointed out during the Sixty-fourth Session of INCB in May 1998.

Licit cultivation of the opium poppy is reported by 16 countries, the seeds of which are traded internationally. Poppy straw, which was once a useless by-product of poppy cultivation, has become an important source of morphine and related alkaloids. In a few countries, poppy straw is used for decorative purposes. There is also some international trade in poppy straw. Although strict control measures apply to the cultivation of the opium poppy for the production of opium, its cultivation for other purposes is not subject to the same degree of regulation.

In the past decoction of poppy capsules was used as a hypnotic. Abuse by opiate abusers was also well known. Since the late 1970s, a new method has been used to prepare poppy straw extract; this involves the hot water extraction of alkaloids from the poppy straw, followed

by concentration of the extract and treatment of the residue with an acetylating agent (acetic anhydride or concentrated acetic acid). The resulting liquid, administered by intravenous injection, is used in a number of countries in Central and Eastern Europe, where it has led to the development of health problems commonly associated with intravenous drug abuse, such as the spread of human immunodeficiency virus (HIV) infection.

Recommendation

In considering poppy straw, the Committee noted that there are some varieties of opium poppy which contain only negligible concentrations of opiates. The Committee further noted that the poppy straw extracts that are actually abused are already controlled under the 1961 Convention because these extracts meet the definition of a "preparation" (a mixture, solid or liquid containing a drug controlled under the 1961 Convention). An INCB survey has documented that poppy straw can be readily converted into such preparations. However, there are no data to suggest that its conversion into a drug already in Schedule I or II of the 1961 Convention has become any easier than previously. Since the scheduling criterion would require poppy straw to be readily convertible to a controlled drug, the Committee did not recommend critical review.

5.8 Tramadol (INN)

Tramadol is a synthetic analgesic used for the treatment of moderate to moderately severe pain. The mechanisms of action reported in the literature are: binding of the parent drug and the *O*-demethylated metabolite (M1) to μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin. The opioid activity of tramadol is due primarily to the high affinity of the M1 metabolite for μ-opioid receptors. In preclinical models, the M1 metabolite is 200–300 times as potent as tramadol in binding to μ-opioid receptors and up to 6 times as potent in producing analgesia. In several tests in animals, analgesia has been shown to be partially antagonized by the opiate antagonist naloxone. Analgesia in humans begins approximately 1 hour after administration and reaches a peak within approximately 2–3 hours, consistent with the formation of the M1 metabolite.

In clinical studies, tramadol has been given in single oral doses of 50, 75, 100, 150 and 200 mg to patients with pain following surgical procedures or oral surgery (extraction of impacted molars). A dose of 100 mg generally produced analgesia superior to that induced by 60 mg of codeine sulfate, but the same dose was not as effective

as the combination of 650mg of aspirin and 60mg of codeine phosphate.

The available data from self-administration, drug discrimination and dependence studies in animals did not show any similarity between tramadol and opioids. Furthermore, the analgesic activity of tramadol in the single hot plate test that was conducted was only modest; however, the M1 metabolite, which has pronounced μ-selectivity, was not tested. With respect to in vitro receptor binding experiments, the M1 metabolite was 20–40 times as potent as codeine and 160–300 times as potent as tramadol in binding to the μ-opioid receptor; morphine was 7–12 times as potent as the M1 metabolite.

Clinically, tramadol has been associated with craving, drug-seeking behaviour and the development of drug tolerance. Cases of abuse and dependence have been reported. Treatment with tramadol is not recommended in patients with a tendency to drug abuse or with a history of drug dependence or chronic use of opioids. If the drug is discontinued abruptly, a withdrawal syndrome (characterized by anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhoea, upper respiratory symptoms, piloerection and, rarely, hallucinations) may result. Withdrawal symptoms in neonates have also been described in the literature. As of September 1999, the WHO Adverse Drug Reactions database had received 236 reports on tramadol dependence, placing it sixth in the list of all drugs for which dependence has ever been reported as an adverse drug reaction. Tramadol ranks eighth in the list of all medicines for which withdrawal syndrome has ever been reported to the WHO Drug Monitoring Programme (with 222 reports received by September 1999) and second in the list of all drugs for which euphoria has ever been reported (80 reports by September 1999).

Recommendation

In humans, tramadol has the potential to produce dependence of the morphine-type (μ-opioid). In terms of the number of cases of withdrawal syndrome and dependence reported as adverse drug reactions to the WHO drug monitoring programme, tramadol is ranked among the first 10 drugs. Cases of abuse have also been reported. Convulsions have been reported after the first dose, in the recommended dosage range, and at higher doses. The risk of occurrence of convulsions is increased in patients taking concomitant medications that may reduce the threshold for seizures (e.g. certain tricyclic compounds and selective serotonin reuptake inhibitors) and in certain medical conditions. For these reasons, the Committee recommended critical review of tramadol.

6. Other matters

Reports from Member States constitute an essential source of data for the assessment of public health and social problems associated with drugs under review for possible scheduling under international conventions. The Committee is concerned that many countries fail to provide WHO with the necessary data for such assessments. The Committee proposed that collaboration between WHO and its Member States be strengthened in this important matter. The Committee also encouraged WHO to seek relevant information directly from INCB, the International Criminal Police Organization (Interpol) and the United Nations International Drug Control Programme (UNDCP).

Acknowledgements

The Committee wishes to acknowledge the contribution made to its discussions by Ms J. Hillebrand and Dr V.B. Poznyak, Mental and Behavioural Disorders, Mental Health and Substance Dependence, WHO, Geneva, Switzerland.

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Annex

Interpretation guidelines concerning the stereoisomers of substances in Schedules II, III and IV of the 1971 Convention[1]

1. These guidelines were elaborated in response to the Decision 42/2 of the United Nations Commission on Narcotic Drugs in order to clarify the scope of control of stereoisomers of substances in Schedules II, III and IV of the 1971 Convention.

2. When the substance listed can exist as stereochemical variants the following should apply:
   (i) if the chemical designation of the substance used in the 1971 Convention (or in a subsequent scheduling decision of the Commission on Narcotic Drugs) does not include any stereochemical descriptors or indicates a racemic form of the substance:
      (a) if the molecule contains one chiral centre, both the *R*- and *S*-enantiomers and the *RS*-racemate are controlled, unless specifically excepted by a decision of the Commission on Narcotic Drugs;
      (b) if the molecule contains more than one chiral centre, all the diastereoisomers and their racemic pairs are controlled, unless specifically excepted by a decision of the Commission on Narcotic Drugs;
   (ii) if the chemical designation used in the 1971 Convention (or in a subsequent scheduling decision of the Commission on Narcotic Drugs) for the substance which contains one chiral centre in the molecule includes a stereochemical descriptor indicating a specific enantiomer, the racemic form of the substance is also controlled, unless specifically excepted by a decision of the Commission on Narcotic Drugs, while the other enantiomer is not controlled;
   (iii) if the chemical designation used in the 1971 Convention (or in a subsequent scheduling decision of the Commission on Narcotic Drugs) for the substance which contains more than one chiral centre in the molecule includes stereochemical descriptors indicating a specific diastereoisomer, only that diastereoisomer is controlled.

[1] Also applicable to Schedule I, in addition to the clarifying phrase that was added to it by the Commission on Narcotic Drugs.

3. When one enantiomer is controlled, then a mixture of that enantiomer with the other enantiomeric substance is controlled.

4. The chemical designations and INNs used in the scheduling decisions to define substances in Schedules II, III and IV of the 1971 Convention were considered appropriate at the times when such decisions were made. It should be understood that:
   (i) alternative chemical designations constructed according to modified chemical nomenclature rules may be used in official documents as long as they preserve the stereospecificity when appropriate;
   (ii) if any subsequent modification of an INN definition uses a chemical designation which is different to that in the scheduling decision, such an INN should be omitted from official documents.